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The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclo-oxygenase-2-selective inhibitor

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SUMMARY

Background
The effect of low-dose aspirin on endoscopic ulcer incidence in cyclo-oxygenase-2-selective inhibitor or non-selective non-steroidal anti-inflammatory drug users remains controversial.

Aim
To compare prospectively the incidence of endoscopic ulcers in healthy subjects receiving low-dose aspirin plus celecoxib or naproxen.

Methods
In this double-blind, placebo-controlled, 1-week study, subjects (50–75 years) were randomized to receive aspirin 325 mg o.d. plus either celecoxib 200 mg o.d., naproxen 500 mg b.d., or placebo. Baseline and end of study endoscopies were performed. The primary end point was incidence of one or more gastric and duodenal ulcers.

Results
A lower incidence of gastric and duodenal ulcers was seen in celecoxib/aspirin-treated subjects (19%) vs. naproxen/aspirin (27%; RR: 0.63, 95% CI: 0.44–0.92). Both naproxen/aspirin and celecoxib/aspirin groups demonstrated a higher incidence of gastric and duodenal ulcers vs. placebo/aspirin (8%; RR: 3.7, 95% CI: 1.8–7.6 and RR: 2.6, 95% CI: 1.2–5.8, respectively).

Conclusions
Fewer endoscopic ulcers were observed in patients treated with celecoxib/aspirin vs. naproxen/aspirin. However, celecoxib/aspirin was associated with a significantly higher incidence of gastric and duodenal ulcers than aspirin alone. Further studies are required to determine the generalizability of these findings in the aspirin users and to determine the appropriate strategy to minimize risk in susceptible patients.

INTRODUCTION

The antithrombotic effects of so-called 'low-dose' aspirin (≤325 mg/day) are well established, and it is widely used for primary and secondary prevention of cardiovascular events, particularly in the older population.[1–4] Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are also prescribed frequently in older patients for the treatment of rheumatic diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA).[5] However, it is well known that non-selective NSAIDs are associated with a heightened incidence of gastric and duodenal ulcer complications,[6–8] and increasing age is a recognized risk factor for these complications.[9–11]

Aspirin effects platelet and endothelial function through thromboxane A_2 (TxA_2) and prostacyclin (PGI_2) pathways respectively.[4, 12, 13] It is believed that use of low-dose aspirin and its antithrombotic effect is beneficial for patients at heightened cardiovascular risk. However, aspirin also inhibits cyclo-oxygenase (COX)-1 activity in the gastric mucosa[4, 14, 15] and has been found to be associated with an endoscopic gastric and/or duodenal ulcer prevalence of 11% at doses of 75–325 mg o.d.[16] Beyond endoscopic ulcers, aspirin is also associated with a dose-related propensity for the development of clinically significant gastric and duodenal ulcer complications.[17–20]

Concurrent administration of aspirin with non-selective NSAIDs is reported to be associated with substantial increases in the risk of upper gastrointestinal (GI) haemorrhage compared with administration of each drug alone.[18] COX-2-selective inhibitors are associated with significantly lower rates of upper GI events and endoscopic ulcers compared with non-selective NSAIDs in the absence of aspirin use,[21–27] but controversy continues to surround the issue of whether their GI safety benefit persists in the setting of low-dose aspirin co-therapy.[24, 25] Several endoscopic studies[28–30] have provided conflicting results compared with outcomes studies[24, 25, 31] regarding the relative and absolute risks associated with co-therapy of aspirin and COX-2-selective inhibitors.

Given the discrepancies between endoscopic data and large outcomes trials, the present prospective study was designed to further investigate the short-term GI effects of a COX-2-selective inhibitor plus aspirin in an age-relevant population. We performed a multicentre, double-blind, randomized study to determine the incidence of gastric and duodenal endoscopic ulcers in healthy subjects aged 50–75 years receiving aspirin (325 mg o.d.) plus celecoxib, naproxen, or placebo.

MATERIALS AND METHODS

Study design

This was a 7-day, multicentre, randomized, double-blind, double-dummy, active comparator and placebo-controlled, parallel group study. Volunteers were recruited from 39 centres in the United States. The protocol was approved by the Institutional Review Boards at each participating centre, and written informed consent was obtained from each subject prior to study entry and before any study-related procedures were performed.

Patients

Healthy adults aged 50–75 years were eligible for randomization if they had a normal physical examination, normal clinical laboratory test results during the screening visit and if they had ≤5 erosions on baseline endoscopy.

Individuals were excluded from the study if they had: a positive *Helicobacter pylori* serological test (FlexSure *H. pylori* Test, SmithKline Diagnostics, San Jose, CA, USA) at baseline; a gastric, pyloric or duodenal ulcer, or ≥6 erosions in the stomach or duodenum at baseline endoscopy; any oesophageal ulcer or erosion; a history of or active GI disease; or diagnosis or treatment for ulcers within 30 days prior to the first dose of study medication. Volunteers were also excluded if they had used any over-the-counter or prescribed NSAIDs (including aspirin), analgesics or anti-ulcer medication, antacids, systemic steroids or anticoagulants within 2 weeks of the first dose of study medication. Any individual with a known history of chronic alcohol consumption, or alcohol or narcotic abuse were not permitted entry into the study. Women of child-bearing potential were required to have confirmed use of adequate contraception and a negative urine pregnancy test result within 24 h prior to receiving study medication.

Pre-treatment period

At the screening visit, which occurred within 10 days of the first dose of study medication, a full medical history was obtained and each subject underwent a physical examination and clinical laboratory testing, including a complete blood count, alanine amino transferase, aspartate amino transferase, blood urea nitrogen and creatinine. Serological testing for *H. pylori*

was also conducted. Upper GI endoscopy was performed within 24 h prior to administration of study medication at the baseline/randomization visit (day 1). The investigator followed standard procedures for performing upper GI endoscopy and recorded pictures of any lesions visualized. Based on the endoscopy findings, investigators assigned gastric and duodenal mucosal scores according to a predefined 8-point grading scale ranging from 0 to 7, where: 0 = normal mucosa; 1 = 1–10 petechiae; 2 = >10 petechiae; 3 = 1–5 erosions; 4 = 6–10 erosions; 5 = 11–25 erosions; 6 = >25 erosions and 7 = ulcer. Erosions were defined as a lesion with definite discontinuance in the mucosa but without depth. Ulcers were classified as any break in the mucosa ≥3 mm in diameter with unequivocal depth.[32]

Treatment period

Based on a computer-generated process, subjects were randomized according to the order in which they enrolled in the study in a 2:2:1 ratio to celecoxib 200 mg o.d. plus aspirin 325 mg o.d., naproxen 500 mg b.d. plus aspirin 325 mg o.d. or placebo plus aspirin 325 mg o.d. for 7 days. Aspirin was provided to all enrolled subjects in an open-label fashion. Individuals assigned to celecoxib treatment received celecoxib 200 mg capsules and dummy capsules matching naproxen. Subjects randomized to the naproxen arm received naproxen 500 mg capsules and dummy capsules matching celecoxib; subjects randomized to placebo received dummy capsules matching celecoxib and naproxen. All subjects were instructed to take study medication twice daily with a morning and evening meal.

Use of any other drugs in addition to study medication was discouraged during the treatment period. The following drugs were strictly prohibited: NSAIDs and COX-2-selective inhibitors, other than study medication; other prescription or over-the-counter anti-inflammatory or analgesic drugs, including opioids, prescription or over-the-counter anti-ulcer medications and calcium-channel blockers. If considered necessary, subjects were allowed hormone-replacement therapy, vitamin supplements and paracetamol/acetaminophen (up to 500 mg b.d.).

Post-treatment period

Subjects returned for evaluation at day 7 or upon early termination. A second upper GI endoscopy was performed 2–4 h after the morning dose of study medication. For consistency, the same endoscopist, blinded to treatment, carried out baseline and post-treatment endoscopies using the same equipment and measuring devices. Subjects also underwent a physical examination and clinical laboratory tests.

Study end points

The primary study end point was the incidence of gastric and duodenal ulcers, defined as ≥1 gastric, pyloric channel or duodenal ulcer, as determined by upper GI endoscopy on day 7 of treatment. Secondary study end points included the incidence of any gastric or duodenal ulcer (grade 7) and any gastric and duodenal, gastric or duodenal erosion/ulcer (grades 4–7). Adverse events were self-reported and were collected and aggregated for all randomized subjects.

Sample size calculation

In a previous 7-day endoscopy study in healthy subjects, gastric and duodenal ulcer rates were: placebo 0%, celecoxib 100 mg b.d. 0% and naproxen 500 mg b.d. 19%.[33] Using these rates and assuming that aspirin had no effect on ulcer incidence in the naproxen arm, it was determined that a sample size of 164 subjects per group was required to maintain ≥80% power to detect significant differences between celecoxib and naproxen, provided the ulcer incidence in the celecoxib arm did not exceed 8%. These calculations were based on a two-sided Fisher's exact test with a 5% significance level.

Statistical analyses

The endoscopy evaluable population, used for analysis of the endoscopy data, included all randomized patients who received ≥1 dose of study medication and had both baseline and post-treatment endoscopies. All subjects who were randomized and received ≥1 dose of study medication were included in the safety analyses.

Comparability between treatment groups with respect to gender and race was assessed by Cochran-Mantel-Haenszel (CMH) statistics with stratification by centre; two-way analysis of variance with centre and treatment as fixed factors was used to determine comparability between treatment arms with respect to continuous variables such as age and vital signs.

In the primary analysis, incidence of gastric and duodenal ulcers (grade 7) on day 7 was calculated for celecoxib plus aspirin and naproxen plus aspirin groups and was compared using CMH statistics stratified by centre. Secondary analyses involved the comparison of gastric and duodenal ulcer incidence for both active treatment arms vs. placebo plus aspirin, as well as pairwise group comparisons of incidence of gastric and duodenal ulcers (grade 7), gastric and duodenal ulcers/erosions, gastric ulcers/erosions and duodenal ulcers/erosions (grades 4–7) using CMH tests, again stratified by centre.

RESULTS

Patient demographics and disposition

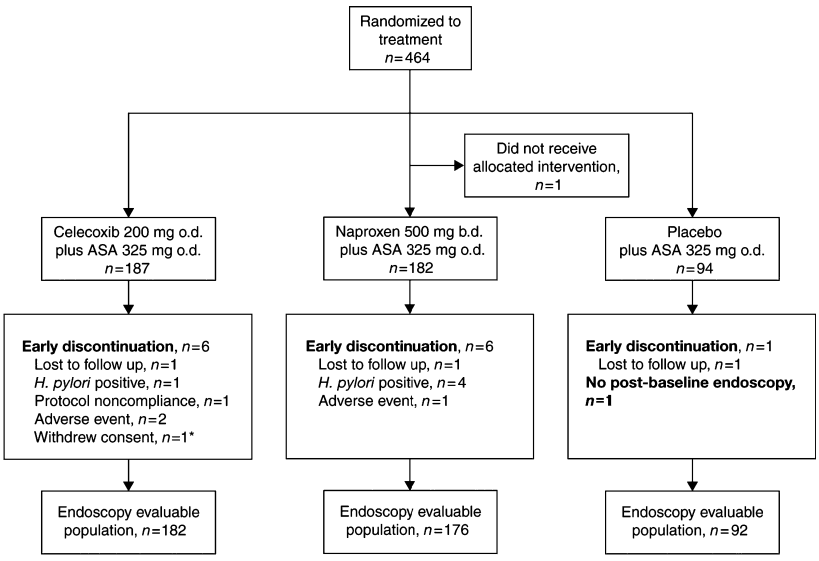
Four hundred and sixty-four subjects were randomized and 463 of these subjects received at least one dose of study medication (187 in the celecoxib plus aspirin group, 182 in the naproxen plus aspirin group and 94 in the placebo plus aspirin group). The single subject who did not receive study medication was randomized to the naproxen plus aspirin group but was identified as having a pre-existing protocol violation (*H. pylori*-positive) and did not proceed in the trial. Across the three arms of the trial, a total of 13 subjects prematurely discontinued study medication and 12 of these did not undergo a post-baseline endoscopy. These 13 subjects included five individuals with a pre-existing protocol violation, who were found to be *H. pylori*-positive, and three who discontinued due to adverse events (two GI adverse events and one vision disorder; none of which was considered serious; Figure 1).

At baseline, the treatment arms were well matched with respect to demographics and baseline endoscopy findings for the randomized population (Table 1). Subjects ranged in age from 50 to 75 years, with a mean age of approximately 57 years, and were predominantly Caucasian (77–84%) and female (55–65%). Medical history was similar between treatment arms. Less than 3% of subjects in any group had a history of a gastric and duodenal ulcer and none had a history of upper GI bleeding.

No statistically significant differences were observed in the mean pre-treatment gastric and duodenal endoscopy results across all three groups ($P \geq 0.08$, Table 1).

Primary end point

During this 1-week study, analysis of the endoscopy evaluable population demonstrated that significantly fewer subjects in the celecoxib plus aspirin group developed ≥1 gastric and duodenal ulcer compared with the naproxen plus aspirin group [relative risk (RR): 0.63, 95% CI: 0.44–0.92; $P = 0.016$; Figure 2a]. The number-needed-to-treat (NNT) to prevent one ulcer was 12. A significantly higher proportion of subjects in the celecoxib plus aspirin group developed gastric and duodenal ulcers compared with the placebo plus aspirin-treated subjects (RR: 2.6, 95% CI: 1.2–5.8;



*Included in the endoscopy evaluable population as subject underwent a post-baseline endoscopy.

Figure 1. Subject disposition.

Table 1. Demographics and baseline characteristics – randomized population

	Celecoxib 200 mg o.d. plus ASA 325 mg o.d. ($n = 187$)	Naproxen 500 mg b.d. plus ASA 325 mg o.d. ($n = 183$)	Placebo plus ASA 325 mg o.d. ($n = 94$)	P-value
Age (years; mean ± s.d.)	56.7 ± 5.8	56.5 ± 5.9	57.2 ± 7.1	0.738*
Female, *n* (%)	119 (63.6)	101 (55.2)	61 (64.9)	0.094†
Race, *n* (%)				
Caucasian	149 (79.7)	153 (83.6)	72 (76.6)	0.308†
Black	11 (5.9)	6 (3.3)	8 (8.5)	
Asian	5 (2.7)	1 (0.5)	2 (2.1)	
Native American	1 (0.5)	0 (0)	0 (0)	
Hispanic/Latin American	21 (11.2)	21 (11.5)	11 (11.7)	
Other	0 (0)	2 (1.1)	1 (1.1)	
Medical history, *n* (%)				
Gastric and duodenal ulcers	2 (1.1)	3 (1.6)	2 (2.1)	0.670†
Angina	1 (0.5)	2 (1.1)	0 (0)	0.606†
Coronary artery disease	1 (0.5)	1 (0.5)	0 (0)	0.782†
Myocardial infarction	1 (0.5)	0 (0)	0 (0)	0.472†
Other cardiovascular history	17 (9.1)	18 (9.8)	6 (6.4)	0.499†
Musculoskeletal disease	48 (25.7)	56 (30.6)	27 (28.7)	0.585†
Mean pre-treatment endoscopy lesions (±s.d.)				
Gastric mucosa				
Number of petechiae	1.0 (±3.5)	0.6 (±1.8)	1.2 (±7.8)	0.487*
Range	0–30	0–10	0–72	
Number of erosions	0.2 (±0.8)	0.2 (±0.7)	0.2 (±0.8)	0.974*
Range	0–5	0–4	0–5	
Duodenal mucosa				
Number of petechiae	0.3 (±1.4)	0.3 (±1.6)	0.1 (±1.0)	0.453*
Range	0–11	0–15	0–10	
Number of erosions	0.1 (±0.3)	0 (±0.1)	0 (±0)	0.079*
Range	0–3	0–1	0	

ASA, aspirin.
* P-value from two-way analysis of variance with centre and treatment as fixed effects.
† P-value from Cochran-Mantel-Haenszel test stratified by centre.

$P = 0.008$; Figure 2a). A higher incidence of gastric and duodenal ulcers was also observed in naproxen-treated subjects compared with the placebo group (RR: 3.7, 95% CI: 1.8–7.6; $P < 0.001$).

Secondary end points

At the post-treatment endoscopy, more gastric ulcers were observed in the naproxen plus aspirin (RR: 3.3, 95% CI: 1.5–7.3; $P = 0.002$; Figure 2b) and celecoxib plus aspirin groups (RR: 2.7, 95% CI: 1.2–6.4; $P = 0.012$) compared with the placebo group. The incidence of gastric ulcers in the celecoxib treatment arm was numerically lower than the naproxen group, but this difference was not significantly different (RR: 0.79, 95% CI: 0.52–1.2; $P = 0.269$; Figure 2b). Duodenal ulcers were less common than gastric ulcers in all treatment groups and developed in significantly fewer subjects treated with celecoxib plus aspirin compared with naproxen (RR: 0.40, 95% CI: 0.17–0.94; $P = 0.027$; Figure 2c). Comparisons with the placebo plus aspirin group showed that subjects treated with naproxen were more likely to develop endoscopic duodenal ulcers (RR: 9.9, 95% CI: 1.2–83.9; $P = 0.006$), and a numeric trend was apparent for celecoxib (RR: 5.1, 95% CI: 0.59–44.5; $P = 0.095$; Figure 2c).

Other secondary end points (incidence of gastric and duodenal ulcers/erosions) supported the results of the primary analysis (Figure 3).

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